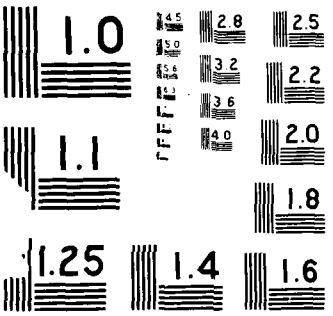
AD-A207 593 SELECTABLE SETS OF NOVEL PROTEINS: CATALYTIC AND OTHER PROPERTIES(U) PENNSYLVANIA UNIV PHILADELPHIA DEPT OF BIOCHEMISTRY S A KAUFFMAN 08 MAY 89 N00014-85-K-0258 1/1

UNCLASSIFIED F/G 6/2 NL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SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved OMB No 0704-0188

1a REPORT SECURITY CLASSIFICATION: Unclassified

1b RESTRICTIVE MARKINGS:

3 DISTRIBUTION / AVAILABILITY OF REPORT: Unlimited

AD-A207 593

S)

5 MONITORING ORGANIZATION REPORT NUMBER(S):

6a NAME OF PERFORMING ORGANIZATION	6b OFFICE SYMBOL (If applicable)	7a NAME OF MONITORING ORGANIZATION
Univ of PA Sch of Medicine Department of Biochemistry		

6c. ADDRESS (City, State, and ZIP Code)	7b. ADDRESS (City, State, and ZIP Code)
36th & Hamilton Walk Philadelphia, PA 19104	

8a. NAME OF FUNDING / SPONSORING ORGANIZATION	8b. OFFICE SYMBOL (If applicable)	9 PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
Office of Naval Research	N00014	N00014-85-K-0258 PRIME P04

8c. ADDRESS (City, State, and ZIP Code)	10 SOURCE OF FUNDING NUMBERS			
	PROGRAM ELEMENT NO	PROJECT NO	TASK NO	WORK UNIT ACCESSION NO
Chemistry Division , 800 N. Quincy St. Arlington, VA 22217				

11. TITLE (Include Security Classification)
Selectable Sets of Novel Proteins: Catalytic and Other Properties (unclassified)

12. PERSONAL AUTHOR(S)
Kauffman, Stuart A.

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15 PAGE COUNT
Final End-ofYear	FROM 7/1/88 TO 9/30/88	1989, May 8	8

16 SUPPLEMENTARY NOTATION

17 COSATI CODES			18 SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	evolution, recombinant DNA, proteins, peptides, selection, adaptation, catalysis

19 ABSTRACT (Continue on reverse if necessary and identify by block number)

This proposal aimed at the development of mathematical, computer, recombinant DNA, selection and screening procedures to attain adaptive evolution of entirely novel peptides or fusion proteins with useful catalytic, ligand binding, structural or other features. Potential uses range from industrial catalysis to production of new drugs and vaccines. A broad purpose of the experimental effort is to obtain novel peptides which can mimic the biological effects of almost arbitrary signal molecules such as hormones, growth factors, even pathogenic antigens. Mathematical models were developed to explore rugged "adaptive landscapes" associated with protein evolution. The fundamental importance of this work includes analysis of the distribution of function in peptide space and opening the way towards a technology of applied molecular evolution.

20 DISTRIBUTION / AVAILABILITY OF ABSTRACT	21 ABSTRACT SECURITY CLASSIFICATION
☐ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT ☐ DTIC USERS	Unclassified

22a NAME OF RESPONSIBLE INDIVIDUAL	22b TELEPHONE (Include Area Code)	22c OFFICE SYMBOL
Dr. Stuart A. Kauffman	215-898-8731	

DD Form 1473, JUN 86 Previous editions are obsolete

S/N 0102-LF-014-6603

Office of Naval Research

Final Report

Publications/Patents/Presentations/Honors/Students Report

for

Contract # N00014-85-K-0258 PRIME PO4

Selectable Sets of Novel Proteins:
Catalytic and Other Properties

Stuart A. Kauffman
Principal Investigator

Department of Biochemistry & Biophysics
University of Pennsylvania School of Medicine
Philadelphia, PA 19104

Part I

a. Papers Submitted to Refereed Journals

E. D. Weinberger, A More Rigorous Derivation of Some Properties of Uncorrelated Fitness Landscapes, J. Theor. Biol., 1988.

Kauffman, S.A. Adaptation on rugged fitness landscapes. In: Complex Systems, SFI studies in the science of complexity. D. Stein, ed. New York: Addison-Wesley Longman, 1988.

Kauffman, S.A. Principles of adaptation in complex systems. In: Complex Systems, SFI studies in the science of complexity. D. Stein, ed. New York: Addison-Wesley Longman, 1988.

b. Papers Published in Refereed Journals

Kauffman, S.A. Origins of Order in Evolution: Self Organization and Selection. In: Biomathematics and Related Computational Problems. L.M. Ricciardi ed. Kluwer Academic Publishers (1988).

Kauffman, S.A., E. Weinberger and A.S. Perelson. Maturation of the Immune Response via Adaptive Walks on Affinity Landscapes. In: Theoretical Immunology, Part One, Santa Fe Institute Studies in the Science of Complexity. P.W. Anderson, K.J. Arrow and K. Pines, eds. Addison-Wesley (1988) p.399-380.

Kauffman, S.A. The Evolution of Economic Webs. In: The Economy as an Evolving Complex System, Santa Fe Institute Studies in the Sciences of Complexity. P.W. Anderson, K.J. Arrow and D. Pines, eds. Addison-Wesley (1988) p.125-146.

c. Books (and sections thereof) Submitted for Publication

S.A. Kauffman. Origins of Order: Self Organization and Selection in Evolution, Oxford University Press.

d. Books (and sections thereof) Published

None.

e. Technical Reports and Papers Published in Non-Refereed Journals

ONR End-of-Year Report July 1988, (this contract).

f. Patents Filed

None.

g. Patents Granted

None.

h. Invited Presentations at Conferences

S.A. Kauffman, Complex Systems Summer School, Santa Fe Institute, Santa Fe, NM, June 9-July 8, 1988.

S.A. Kauffman, NATO Advanced Research Workshop: Theoretical Models for Cell to Cell Signaling, Knokke-Zoute, Belgium, Sept 4-9, 1988.

i. Contributed Presentations at Conferences

None.

j. Honors/Awards/Prizes

None.

k. Number of Graduate Students Receiving Full or Partial Support on ONR Contract

1. Thomas Labean

2. Lloyd Clark

l. Number of Postdoctoral Fellows Receiving Full or Partial Support on ONR Contract

1. Edward D. Weinberger

m. Manuscripts in Preparation

S.A. Kauffman, L. Clark and E. Weinberger. The NK model of random epistatic interactions: Landscape structure.

S.A. Kauffman and L. Clark, The NK model: Population flow on a tunably rugged fitness landscape.

Part II

a. Principal Investigator

Stuart A. Kauffman

b. Cognizant ONR Scientific Officer

Barbury Schmidt

c. Current Telephone Number

215-898-8731

d. Brief Description of Project

1. The generation and cloning of a very large library of pseudo-random DNA coding sequences into an expression vector.

2. Demonstration that the pseudo-random sequences code for and lead to the synthesis of novel peptides or fusion proteins.

3. Attempt to select for catalytic or other function by the novel peptides.

4. Explore mathematical models of rugged "adaptive landscapes" associated with protein evolution.

e. Significant Results

Points 1. and 2. part d., above, have been achieved. A library with 10,000,000,000 novel pseudo-random coding sequences has been obtained and statistically characterized. Point 3. has not been accomplished. We selected for viral vectors with novel genes which conferred resistance to gentamicin and chloramphenicol in E.coli hosts, found such resistance but have been unable to confirm the case where the resistance is due to the novel gene. Point 4. We have developed a spin-glass like model of rugged but correlated fitness landscapes. The model allows us to predict features of the adaptive "maturation" of the immune response by rapid accumulation of somatic mutants in antibody variable regions improving the affinity of the antibody molecule for the in coming antigen.

f. Summary of Future Plans

We plan to clone other novel peptides into new vectors. One plan is to use a vector which allows synthesis of the novel peptide free of inclusion in a fusion protein. We will begin to ask whether pseudo-random peptides or proteins can fold reliably into a compact shape with the hope of understanding the protein folding process. We will attempt to clone novel protein sequences into vectors that will display novel peptides on cell surfaces and test whether we can find novel peptides which mimic a specific antigen by cross-reactivity to a common antigen. Such peptides could become drugs or vaccines. We also hope to clone into a secretion vector and ask if secreted peptides can act to close autocrine feedback loops leading to self-stimulating growth of cells. This is the subject of my new patent application.

Work on rugged landscapes and combinatorial optimization is the subject of a separate proposal to ONR in which we have received additional funding (Contract #N00014-89-J-1623).

g. List of names of graduate students and post-doctorals currently working on the project.

Thomas LaBean, graduate student

Lloyd Clark, graduate student

Edward D. Weinberger, research associate

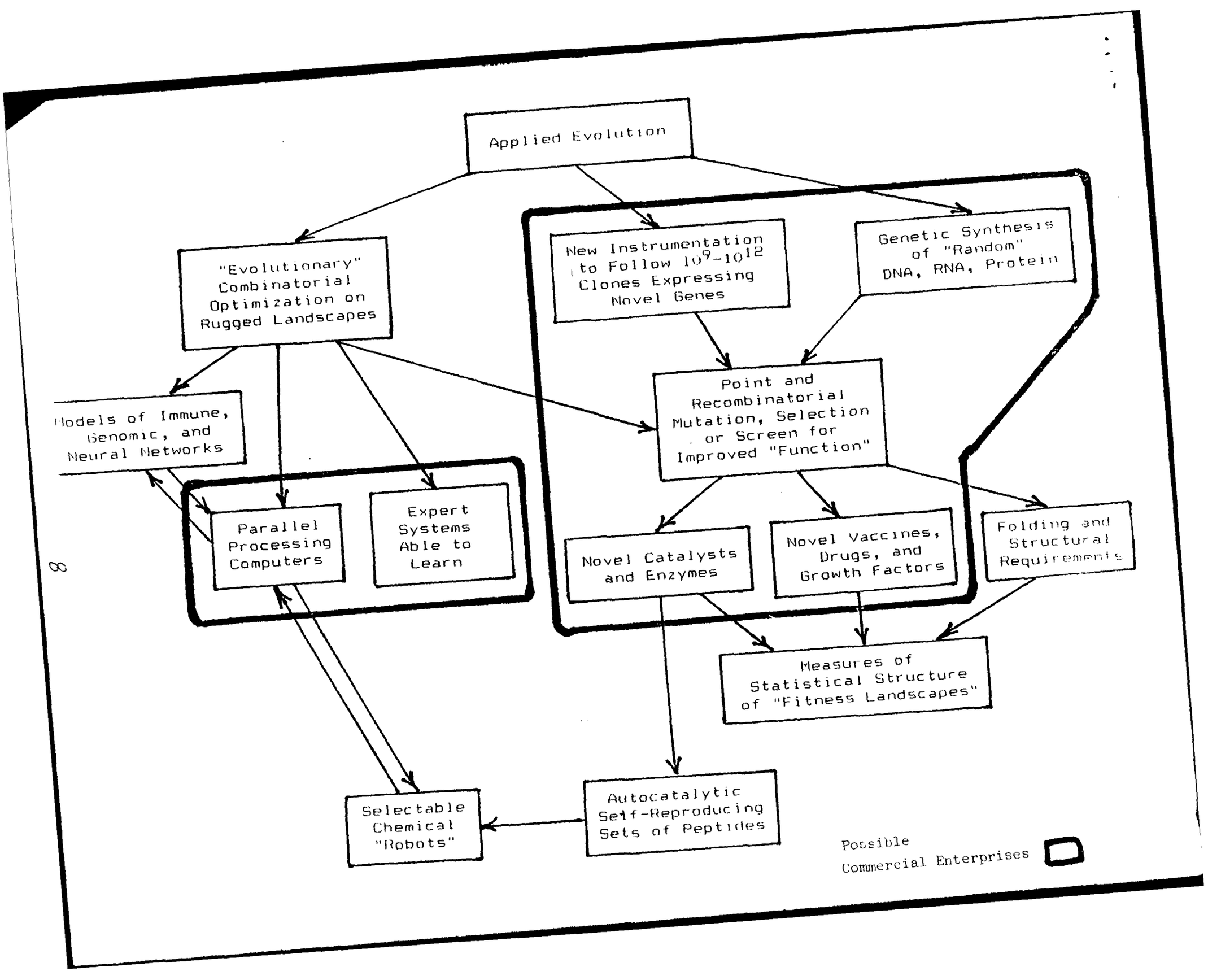
h. Technical reports submitted to ONR

End-of-Year report July 1988, (this contract).

End-of-Year report June 1989,
(new contract #N00014-89-J-1623)

Part III

This proposal aimed at the development of mathematical, computer, recombinant DNA, selection and screening procedures to attain adaptive evolution of entirely novel peptides or fusion proteins with useful catalytic, ligand binding, structural or other features. Potential uses range from industrial catalysis to production of new drugs and vaccines. A broad purpose of our experimental efforts is to obtain novel peptides which can mimic the biological effects of almost arbitrary signal molecules such as hormones, growth factors, even pathogenic antigens. The fundamental importance of this work includes analysis of the distribution of function in peptide space and opening the way towards a technology of applied molecular evolution.


Applied Evolution
"Evolutionary" Combinatorial Optimization on Rugged Landscapes
New Instrumentation to Follow 10^9–10^{12} Clones Expressing Novel Genes
Genetic Synthesis of "Random" DNA, RNA, Protein
Point and Recombinatorial Mutation, Selection or Screen for Improved "Function"
Models of Immune, Genomic, and Neural Networks
Parallel Processing Computers
Expert Systems Able to Learn
Novel Catalysts and Enzymes
Novel Vaccines, Drugs, and Growth Factors
Folding and Structural Requirements
Measures of Statistical Structure of "Fitness Landscapes"
Selectable Chemical "Robots"
Autocatalytic Self-Reproducing Sets of Peptides
Possible Commercial Enterprises

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